111-1030.00-DHC

ATTENTION: BOX PATENT EXTENSION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#7

In re United States Patent No. 4,303,651

Patentees: Ulf P.F. Lindahl
Gudrun E. Bäckström
John Y.L. Thunberg
Lars-Åke Fransson
Lars-Olov Andersson
Erik Y. Holmer
Inga H. Sandberg
Ewa G. Söderström

Assignee: Pharmacia Aktiebolag

Issue Date: December 1, 1981

Filing Date: January 4, 1980

REQUEST AND APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. 156 FOR U.S. PATENT NO. 4,303,651

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984 and as amended, 35 U.S.C. 156, Pharmacia Aktiebolag, owner of the above-identified patent by an assignment recorded on January 4, 1980 at Reel 3726, Frame 819 to Kabi AB (Exhibit 12) and subsequent change of corporate name recorded on August 10, 1992 at Reel 6223, Frames 645-647 (Exhibit 13) and subsequent merger recorded January 6, 1995 at Reel 7235, Frames 329-335 (Exhibit 14) hereby requests an extension of the patent term of U.S. Patent No. 4,303,651. The following information is submitted in

accordance with 35 U.S.C. 156(d) and 37 C.F.R. 1.710 et seq., and follows the numerical format set forth in 37 C.F.R. 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is Dalteparin Sodium Injection, sold under the trademarks Fragmin™, e.g., in Germany, United Kingdom, Sweden, Japan, and Australia and Fragmine™ in France. The trade name Fragmin™, will be used also in the United States after registration of the product. The approved product has the following physical structure and characterization:

International non-proprietary name (INN), WHO list No. 31, British approved name (BAN), as well as U.S. adopted name (USAN): Dalteparin Sodium.

Chemical name: Sodium salt of depolymerized heparin obtained by nitrous acid degradation of heparin from pork intestinal mucosa. The majority of the components have a 2-O-sulfo α-L-idopyranosuronic acid structure at the non-reducing end and a 6-O-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The degree of sulfation is 2 to 2.5 per disaccharidic unit.

Other names: Heparin sodium (low molecular weight), average molecular weight 5000, Low Molecular Weight Heparin (LMWH), and Low-molecular-mass Heparins (LmmH).

Laboratory code: Heparin Fragment Kabi 2165.

Relative molecular mass: The average relative molecular mass is about 5000, 90 percent of which ranging between 2000 and 9000.

Structural formula: The structural formula is evident from Exhibit 1.

2) A complete identification of the Federal statute, including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FFDCA) and Title 21 of the Code of Federal Regulations (CFR), Part 314.50. Section 505 of FFDCA provides for the submission and approval of new drug applications (NDA's) for human drug products meeting the definition of "new drug" under Section 201(p) of the Act.

3) An identification of the date on which the product received permission for commercial marketing, or use under the provision of law under which the applicable regulatory review period occurred:

Fragmin™ (Dalteparin Sodium Injection) was approved by the Food and Drug Administration (FDA) for manufacture and import into the United States for commercial marketing (sale, barter or exchange) pursuant to Section 505 of the FFDCA on December 22, 1994 (see Exhibit 2).

4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved:

As stated in Sections 1, 2 and 3 above, the active ingredient in the product is Dalteparin Sodium. Dalteparin Sodium had not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act until December 22, 1994.

5) A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to Section 1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on December 22, 1994 (Exhibit 2) and the last day within the sixty-day period for submission of an application for extension of a patent is February 20, 1995. This application is timely filed.

6) A complete identification of the patent for which an extension is being sought by the name of the inventors, the patent number, the date of issue and the date of expiration:

U.S. Patent No.:	4,303,651
Inventors:	Ulf P.F. Lindahl Gudrun E. Bäckström John Y.L. Thunberg Lars-Åke Fransson Lars-Olov Andersson Erik Y. Holmer Inga H. Sandberg Ewa G. Söderström
Issued:	December 1, 1981
Expires:	January 4, 2000 (20 years from the U.S. filing date of January 4, 1980)

7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the patent is attached as Exhibit 3.

8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment or reexamination certification issued in the patent: Not subject to maintenance fees and no disclaimer, no certificate of correction and no reexamination certificate.

9) A statement beginning on a new page that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

U.S. Patent No. 4,303,651 claims the approved product, Fragmin™ (Dalteparin Sodium Injection) and compositions containing the approved product.

As stated in Section 1 above, Fragmin™ (Dalteparin Sodium Injection) is a polydisperse product with about 90% of the material within the molecular mass range of 2000-9000, and with an average molecular mass of 5000 (see especially the structural formula of Exhibit 1, where n = 3-20).

Claims 1 and 3 of U.S. Patent No. 4,303,651 are directed to heparin fragments having 14-18 sugar units. This corresponds to 7-9 disaccharide units (see the structural formula of Exhibit 1). According to Example 1 of U.S. Patent No. 4,303,651, tetradeca-octadecasaccharides correspond to a molecular mass (weight) of from 3600 to 4800. Thus, the product Fragmin™ is covered by claims 1 and 3 as regards the molecular mass.

Claims 1 and 3 further discloses that the main component is the disaccharide unit L-iduronosyl-2-O-sulphate-N-sulpho-D-glucosamine-6-O-sulphate. This corresponds to the structural formula of the repetitive disaccharide unit of the product Fragmin™ (Exhibit 4).

Claims 2 and 4 are directed to L-iduronic acid 2-O-sulphate (U) and N-sulpho-D-glucosamine-6-O-sulphate (G). In the ^{1}H NMR spectrum of Fragmin™ (Exhibit 5, from Pharmacia's Technical Report 91 96 352 included in the NDA file), the H-1 and H-2

protons of the N-sulpho-D-glucosamine-6-O-sulphate (denoted $GlcNSO_3$ ($6S0_3$)) appear as major peaks. Of equal size are the well separated peaks of the H-1 and H-2 protons of the L-iduronic acid-2-O-sulphate. The components denoted U and G can thus also be shown by the ^1H NMR spectrum. Claim 2 is further directed to L-iduronic acid (I), a component which also appears in the ^1H NMR spectrum (denoted H-1 IdoA). Thus, the presence of the structural parts of claims 1 to 4 is evident from the ^1H NMR spectrum of Fragmin™.

The marketing authorization covers a product, Fragmin™ (Dalteparin Sodium Injection) for use in prophylaxis of thrombosis. This is covered by claims 3 and 4, which describe a pharmaceutical composition for preventive treatment of thrombosis. The product, Fragmin™, is going to be sold as a water solution for use as an injectable drug. Thus, claim 5 directed to water as pharmaceutical carrier covers the product Fragmin™.

10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

(i) For a patent that claims a human drug product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number; and the date on which the NDA was approved;

(ii) For a patent that claims a food or color additive, the date a major health or environmental effects test on the additive was initiated and any available substantiation of that date; the date on which a petition for product approval under the Federal Food, Drug & Cosmetic Act was initially submitted and the petition number; and the date on which the FDA published a Federal Register notice listing the additive for use;

(iii) For a patent that claims a medical device, the effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device if no IDE was submitted and any available substantiation of that date; the date on which an application for product approval under Section 515 of the Federal Food, Drug and Cosmetic Act was initially submitted and the number of the application; and the date on which the application was approved.

On August 6, 1992, Pharmacia Aktiebolag (formerly Kabi Pharmacia AB), the assignee of U.S. Patent No.4,303,651, submitted a New Drug Application (NDA) to the FDA, an application submitted under Section 505(b)(1) of the Federal Food, Drug and

Cosmetic Act (FFDCA) and pursuant to Title 21 of the Code of Federal Regulations (CFR) part 314.50 for Fragmin's safe and effective use as prophylaxis against thromboembolic complications in the intra- and post-operative surgical period. The clinical trials have been carried out mainly in Europe.

A copy of the letter transmitting the NDA is attached as Exhibit 6. The NDA submission was received by the FDA on August 7, 1992. FDA advised Pharmacia Aktiebolag on August 11, 1992 that the application was assigned Reference Number NDA 20-287 (see Exhibit 7). A letter refusing to file the NDA under CFR 314.101(d) was issued on September 25, 1992 (see Exhibit 8). Submission of letter addressing the refusal to file issues was sent on December 22, 1992 to the FDA (see Exhibit 9), and receipt acknowledged on December 30, 1992 (see Exhibit 10). Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), February 28, 1993 is the date of the official submission of a new drug application under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Fragmin™ in accordance with 21 CFR 314.101(a).

The NDA described above was approved on December 22, 1994. Attached as Exhibit 2 is a letter dated December 22, 1994 from the FDA to Pharmacia Aktiebolag, approving the NDA for Fragmin™ (Dalteparin Sodium Injection). Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), December 22, 1994, is the date of approval of the application for Fragmin™ submitted on February 28, 1993.

11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, Pharmacia Aktiebolag was actively involved in obtaining NDA approval for Fragmin™. As discussed in Section 10 above, the official submission date of the NDA was February 28, 1993, and the NDA was approved on December 22, 1994. Pharmacia Aktiebolag had numerous contacts and meetings with the FDA with respect to the approval. The description of significant activities undertaken by Pharmacia Aktiebolag with respect to Fragmin™ during the regulatory review period, as set forth in Exhibit 11, is illustrative of the activities involved. Also included in Exhibit 11 is a description of various activities undertaken by Pharmacia Aktiebolag, with respect to Fragmin™, prior to the submission date of the NDA.

12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined.

(a) Statement of eligibility of the patent for extension under 35 U.S.C. 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) The term of U.S. Patent No. 4,303,651 expires on January 4, 2000 in view of 35 U.S.C. 154 as amended (i.e., 20 years from the U.S. filing date of January 4, 1980). This application has therefore been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This application is submitted by the owner of record, Pharmacia Aktiebolag, Assignment recorded on January 4, 1980, at Reel 3726, Frame 819, (Exhibit 12) and subsequent change of corporate name, recorded on August 10, 1992 at Reel 6223, Frames 645-647 (Exhibit 13) and subsequent merger recorded on January 6, 1995, at Reel 7235, Frames 329-335 (Exhibit 14). This application is submitted in accordance with 35 U.S.C. 156(d) in that it is submitted within the sixty-day period beginning on the date, December 22, 1994, the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. 156(d).

(4) As evidenced by the December 22, 1994 letter from the FDA (Exhibit 2), the product was subject to a regulatory review period under Section 505(b)(1) of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of Fragmin™after regulatory review under Section 505(b)(1) of the FFDCA is the first permitted commercial marketing of Fragmin™. This is confirmed by the absence of any approved new drug application or license product application for Fragmin™ prior to December 22, 1994.

(b) Statement as to length of extension claimed:

The term of Patent No. 4,303,651 should be extended by 661 days to October 26, 2001. This extension was determined on the following basis: as set forth in 35 U.S.C. 156(g)(1) and 37 C.F.R. 1.775(c), the regulatory review period equals the length of time between the effective date of the initial IND and the effective submission of the NDA - a period of 0 days since no IND in the United States, plus the length of time between the

effective submission of the NDA (February 28, 1993) to NDA approval (December 22, 1994), a period of 661. These two periods added together equal 661 days.

Pursuant to 35 U.S.C. 156(c) and 37 C.F.R. 1.775(d)(1)(i), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent was issued. In this case, this is a period running from the date of the effective submission of the NDA, February 28, 1993, to the date of NDA approval, December 22, 1994, a period of 661 days.

As discussed in paragraph (11) above and as illustrated in Exhibit 11, Pharmacia Aktiebolag was continuously and diligently working toward securing FDA approval for Fragmin™. As Pharmacia Aktiebolag acted with due diligence during the entire period of regulatory review, the 661 day period calculated above as the term of the patent eligible for extension should not be reduced for lack of diligence under 35 U.S.C. 156(c)(1) or 37 C.F.R. 1.775(d)(1)(ii).

Pursuant to 35 U.S.C. 156(c)(3) and 37 C.F.R. 1.775(d)(2-4), if the period remaining in the term of the patent after the date of approval (December 22, 1994 to January 4, 2000, a period of 1840 days), when added to the revised regulatory review period (661 days) exceeds 14 years (5110 days), the period of extension must be reduced, so that the total of both such periods does not exceed 14 years. In this case, the total of both such periods (2501 days) does not exceed 14 years and therefore, the 661 days revised regulatory review period is not reduced.

The period of patent term extension as calculated above is also subject to the provisions of Section 156(g)(4) and 37 C.F.R. 1.755(d)(5-6). The patent to be extended

issued before the enactment of the statute, September 24, 1984, but no request for exemption as defined in 37 C.F.R. 1.775(d)(6)(i) was filed prior to September 24, 1984. Since commercial marketing of the drug was approved after enactment of the statute, the five year maximum on extension as provided in 35 U.S.C. 156(g)(4)(C) and 37 C.F.R. 1.775(d)(6)(i) is applicable. Thus, the term of the patent is eligible for a 661 day extension until October 26, 2001.

13) The statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought (see Section 1.765):

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought.

14) The prescribed fee for receiving and acting upon the application for extension (see Section 1.20(n)):

As indicated by the letter of transmittal submitted with this application, a check for the filing fee is attached. In addition, the Commissioner of Patents and Trademarks is hereby authorized to charge any fees connected with this communication to Deposit Account No. 22-0185 in the name of Pollock, Vande Sande & Priddy.

15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Address all correspondence to Burton A. Amernick, Pollock, Vande Sande & Priddy, 1990 M Street, N.W., Suite 800, P.O. Box 19088, Washington, D.C. 20036. Direct telephone calls to Burton A. Amernick, 202-331-7111.

16) A duplicate of the application papers, certified as such:

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156, including its attachments and supporting papers, is being submitted with a duplicate copy thereof.

17) An oath or declaration as set forth in 37 C.F.R. 1.740(b):

As the undersigned agent of Pharmacia Aktiebolag, the owner of record of U.S. Patent No. 4,303,651, which, by submission of this paper and attached exhibits, now applies for an extension of term of this patent, I, Christer Wahlström, declare that (1) I am Patent Attorney of Pharmacia Aktiebolag and have general authority from Pharmacia Aktiebolag to act on its behalf in patent matters; that (2) I have reviewed and understand the contents of the attached application for extension of U.S. Patent No. 4,303,651; that (3) I believe the patent is subject to extension pursuant to 37 C.F.R. 1.710; that (4) I believe the length of extension claimed is fully justified under 35 U.S.C. 156 and applicable regulations; and that (5) I believe the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like

so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent extension issuing thereon.

I hereby appoint as United States attorney to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Burton A. Amernick, Registration No. 24,852, said Burton A. Amernick to have in addition full power of revocation.

PHARMACIA AKTIEBOLAG

Date: February 13, 1995

By: Christer Wahlström
Christer Wahlström
Patent Attorney of Pharmacia Aktiebolag

Address all correspondence to Burton A. Amernick, Pollock, Vande Sande & Priddy, 1990 M Street, N.W., Suite 800, P.O. Box 19088, Washington, D.C. 20036. Direct telephone calls to Burton A. Amernick, 202-331-7111.

16) A duplicate of the application papers, certified as such:

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156, including its attachments and supporting papers, is being submitted with a duplicate copy thereof.

17) An oath or declaration as set forth in 37 C.F.R. 1.740(b):

As the undersigned agent of Pharmacia Aktiebolag, the owner of record of U.S. Patent No. 4,303,651, which, by submission of this paper and attached exhibits, now applies for an extension of term of this patent, I, Nats Lidgard, declare that (1) I am General Counsel and Company Secretary of Pharmacia Aktiebolag and have general authority from Pharmacia Aktiebolag to act on its behalf and that (2) I have reviewed and understand the contents of the attached application for extension of U.S. Patent No. 4,303,651; that (3) I believe the patent is subject to extension pursuant to 37 C.F.R. 1.710; that (4) I believe the length of extension claimed is fully justified under 35 U.S.C. 156 and applicable regulations; and that (5) I believe the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like

so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent extension issuing thereon.

I hereby appoint as United States attorney to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Burton A. Amernick, Registration No. 24,852, said Burton A. Amernick to have in addition full power of revocation.

PHARMACIA AKTIEBOLAG

Date: February 14, 1995

By: _____
General Counsel and Company Secretary of Pharmacia Aktiebolag

Date: _____

By: _____
of Pharmacia Aktiebolag

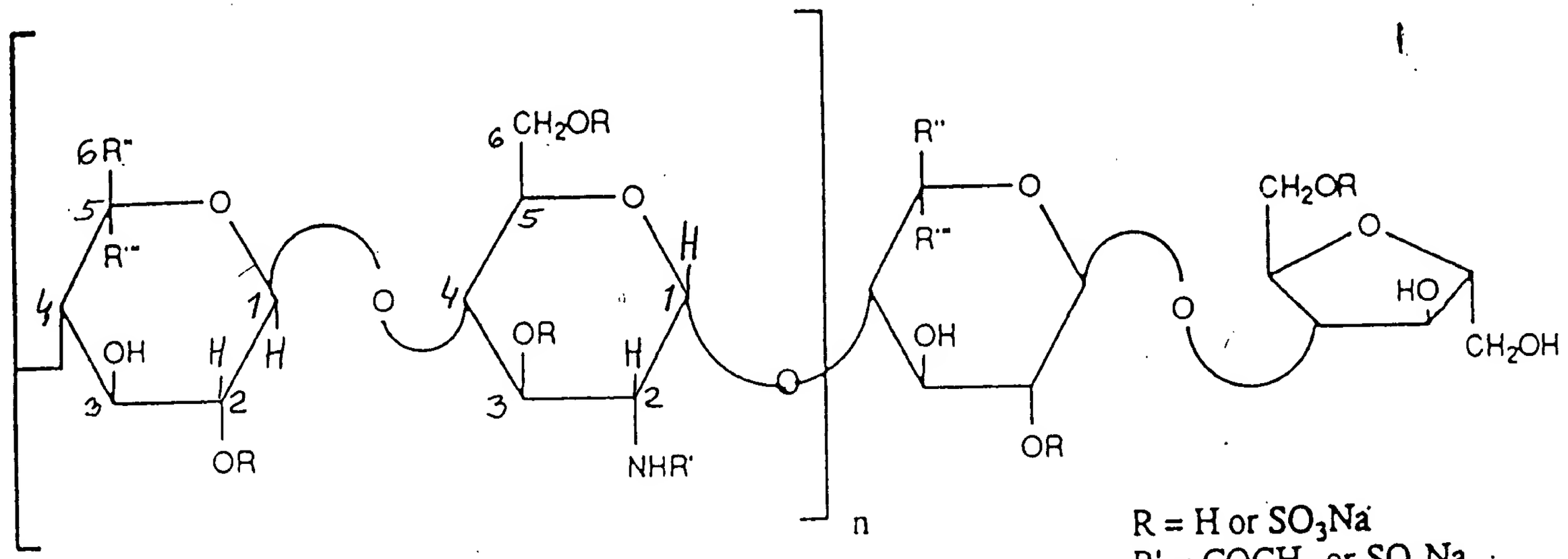
CALCULATION OF LENGTH OF PATENT TERM EXTENSION FOR A HUMAN DRUG PRODUCT

1. ENTER THE NUMBER OF DAYS FOR THE TESTING PHASE AS DEFINED IN 37 CFR 1.775(c) (1)	0	
2. ENTER THE NUMBER OF DAYS FOR THE APPROVAL PHASE AS DEFINED IN 37 CFR 1.775(c) (2)	661	
3. ADD LINE 1 AND LINE 2 AND ENTER THE TOTAL HERE		661
4. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT	0	
5. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775(d) (1) (ii)	0	
6. ADD LINE 4 AND LINE 5 AND ENTER THE TOTAL HERE		0
7. SUBTRACT LINE 6 FROM LINE 3 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")		661
8. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 1 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT	0	
9. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 1 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775(d) (1) (ii)	0	
10. ADD LINE 8 AND LINE 9 AND ENTER THE TOTAL HERE		0
11. SUBTRACT LINE 10 FROM LINE 7 AND ENTER THE DIFFERENCE HERE		661
12. ENTER THE NUMBER OF DAYS FROM LINE 1	0	
13. ENTER THE NUMBER OF DAYS FROM LINE 10	0	
14. SUBTRACT LINE 13 FROM LINE 12 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")	0	
15. MULTIPLY LINE 14 BY 0.5 (ONE HALF) AND ENTER THE AMOUNT HERE		0
16. SUBTRACT LINE 15 FROM LINE 11 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")		661
17. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT	1-4-2000	
18. ENTER THE EXPIRATION DATE OF PATENT IF EXTENDED BY THE NUMBER OF DAYS ON LINE 16	10-26-2001	
19. ENTER THE DATE OF THE FDA (FOOD AND DRUG ADMINISTRATION) FINAL APPROVAL	12-22-94	
20. LIMITATION SET FORTH IN 37 CFR 1.775(d) (3)	14 YEARS	
21. ADD THE NUMBER OF YEARS ON LINE 20 TO THE DATE ON LINE 19 AND ENTER THE REVISED DATE HERE	12-22-2008	
22. ENTER THE EARLIER DATE APPEARING ON LINE 18 OR LINE 21		10-26-2001
23. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)	1-4-2000	
24. CHECK ONE OF THE FOLLOWING THREE BOXES AND ENTER THE LISTED TIME PERIOD HERE	5 years	

		THE PATENT ISSUED AFTER 09/24/84	5 YEARS
	✓	THE PATENT ISSUED PRIOR TO 09/24/84 AND NO REQUEST FOR EXEMPTION AS DEFINED IN 37 CFR 1.775(d) (6) (i) WAS FILED PRIOR TO 09/24/84	5 YEARS
		THE PATENT ISSUED PRIOR TO 09/24/84 AND AN EXEMPTION AS DEFINED IN 37 CFR 1.775(d) (6) (ii) WAS FILED PRIOR TO 09/24/84	2 YEARS

25. ADD THE NUMBER OF YEARS ON LINE 24 TO THE DATE ON LINE 23 AND ENTER THE REVISED DATE HERE	1-4-2005	
26. ENTER THE EARLIER DATE APPEARING ON LINE 22 OR LINE 25		10-26-2001
27. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)		1-4-2000
28. ENTER THE NUMBER OF DAYS BY WHICH LINE 26 AND LINE 27 DIFFER HERE THIS IS THE LENGTH OF PATENT TERM EXTENSION		661

Structural formula



R = H or SO_3Na
R' = $COCH_3$ or SO_3Na
R" = H R''' = COONa
or
R" = COONa R''' = H

n = 3-20

Exhibit 7

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-287

DEC 22 1994

Pharmacia, Inc.
Attention: Dr. Ann Hards
P.O. Box 16529
Columbus, Ohio 43216-6529

Dear Dr. Hards:

Please refer to your August 6, 1992 new drug application and your resubmission dated December 22, 1992 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium) Injection.

We acknowledge receipt of your amendments dated January 12, March 12, June 11 and 22, July 19, August 11, October 12 and 13, November 8, 1993; May 17, 24, and 31, June 24, September 22 and 30, October 11, and December 7, 1994.

This new drug application provides for the use of Fragmin (dalteparin sodium) Injection for prophylaxis of deep venous thrombosis, which may lead to pulmonary embolism, in patients undergoing abdominal surgery who are at risk of thromboembolic complications.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-287. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Bronwyn Collier
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Exhibit 3

United States Patent [19]

Lindahl et al.

[11] **4,303,651**

[45] **Dec. 1, 1981**

[54] **HEPARIN FRAGMENTS HAVING SELECTIVE ANTICOAGULATION ACTIVITY**

[75] Inventors: **Ulf P. F. Lindahl**, Uppsala; **Gudrun E. Bäckström**, Alunda; **John Y. L. Thunberg**, Uppsala; **Lars-Åke Fransson**, Lund; **Lars-Olov Andersson**, Knivsta; **Erik Y. Holmer**, Bromma; **Inga H. Sandberg**, Sollentuna; **Ewa G. Söderström**, Saltsjöbaden, all of Sweden

[73] Assignee: **Kabi AB**, Stockholm, Sweden

[21] Appl. No.: **109,936**

[22] Filed: **Jan. 4, 1980**

[30] **Foreign Application Priority Data**

Jan. 8, 1979 [SE] Sweden 7900164

[51] **Int. Cl.**[3] **A61K 31/725**; C08B 37/10

[52] **U.S. Cl.** **424/183**; 536/21

[58] **Field of Search** 424/183; 536/21

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,066,076	11/1962	Monnier	536/21
3,135,660	6/1964	Bush et al.	536/21
3,810,781	5/1974	Eriksson et al.	424/183
3,835,112	9/1974	Mardiguian et al.	536/21
3,891,622	6/1975	Mardiguian et al.	424/183

Primary Examiner—Johnnie R. Brown

Attorney, Agent, or Firm—Pollock, Vande Sande & Priddy

[57] **ABSTRACT**

Heparin fragments having selective anticoagulation activity having 14–18 sugar units, the disaccharide unit L-iduronosyl-2-O-sulphate-N-sulpho-U-glucosamine-6-O-sulphate being the main component, and where unsulphated L-iduronic acid is in a position situated 3–5 sugar units from the unreducing terminal. Pharmaceutical compositions containing such heparin fragments. Processes for the preparation of the heparin fragments.

6 Claims, No Drawings

HEPARIN FRAGMENTS HAVING SELECTIVE ANTICOAGULATION ACTIVITY

The present invention relates to heparin fragments which have been shown to possess selective anticoagulation activity, a process for the preparation thereof, and therapeutical compositions containing such fragments.

Heparin is a sulphate-containing polysaccharide which on a large scale is isolated from intestinal mucus from swine of lung from cattle. It has for several decades been used clinically as an agent for the treatment and prevention of thrombosis. In spite of the fact that the use of heparin in thrombosis prophylaxis and therapy is still increasing, this form of treatment is far from unproblematic. An important problem is that the dosage must be balanced in such a manner that a good thrombosis protection is obtained simultaneously as bleeding complications are avoided. A difficulty in this contect is the great individual variation between different patients; this is in turn probably dependent on the fact that the heparin is bound to a varying degree to other components in the blood plasma and thereby neutralised. Another problem is that the preventive heparin treatment suffers from limitd success. A third problem with the present type of heparin is its weak effect on arterial thrombosis. At said type of thrombosis the thrombocyte aggregation is a more dominating feature than at the venous thrombosis where heparin gives a good effect. Standard heparin stimulates to a certain extent thrombocyte aggregation and accordingly gives a negative effect in said respect.

The mechanism of the anticoagulation activity of the heparin is now essentially known. The blood coagulation is based on a cascade like process where a number of proteolytic enzymes are activating each other in a definite sequence; in the last stage fibrinogen is converted under the action of the proteolytic enzyme thrombin to insoluble fibrin, the foundamental structure in a blood coagel. Heparin forms a complex with a plasma protein, and this complex inhibits most of the enzymes in the coagulation cascade.

It has been recently shown that heparin fractions of different molecular weights influence the coagulation process in different ways [L.-O. Andersson et al., Tromb. Res. 9, 575 (1976)]. This initiated a study of the possibilities to develop heparin fractions having a more selective action. Treatment of standard heparin with nitrous acid in dimethoxyethane (glyme) at a low temperature and for a certain definite period of time has resulted in a special fragment of heparin possessing a considerably higher selective action than standard heparin. This heparin derivative has a very small effect on the inhibition of thrombin, while the inhibition of activated coagulation factor X is highly accelerated. Coagulation factor X takes a central position in the middle of the coagulation cascade and the inhibition thereof is by many considered especially important to obtain an effective thromsis-preventing effect [S. Wessler, Thromb. Diath. Haemorrh. 33, 81 (1974)].

It has further quite unexpectedly been shown that said type of fragments are not neutralised by the blood components to the same extent as standard heparin. This results in, inter alia, a more efficient utilisation of the anticoagulation activity of this type of fragments compared to the present clinically used heparin preparations. Further, also the dosage is easier to perform, as

the individual variation of heparin-neutralising effect is less important to take into consideration. A further surprising property of the fragment is that its thrombocyte aggreation-inducing activity is much lower than that which is usually shown by heparin. Therefore, it is probable that this type of fragment is a better anticoagulation agent than standard heparin for preventive treatment and treatment of arterial thromboses. It may also be assumed that the reduced influence on the thrombocytes may lead to a lowered risk of bleeding complications.

It should also be noted that the capacity of the heparin to release the enzyme lipoprotein lipase is strongly dependent on the molecular weight. Therefore, it may be assumed that the low molecular weight heparin fragment has a further valuable property in that it to a lesser extent than standard heparin increases the contents of free fatty acids in the blood.

This speical type of heparin fragments may be prepared in several different ways. One of the methods (a) comprises treatment of standard heparin with nitrous acid in dimethoxyethane as mentioned above. Said method gives this type of fragments together with a series of inactive fragements. The active fragments may then be freed from inactive elements, such as by affinity chromatography on matrix-bound antithrombin III [Höök et al., FEBS Lett. 66, 90 (1976); Hopwood et al., FEBS Lett. 63, 51 (1976); L.-O. Andersson et al., Thromb. Res. 9, 575 (1976)]. other ways of preparing fragments are: (b) via periodate oxidation at low pH and low temperature; (c) via partial depolymerisation with heparinase; (d) via partial depolymerisation of heparin by esterification of carboxyl groups and subsequent alkaline β-elimination; (e) via partial depolymerisation of heparin by partial N-desulphatation and subsequent deamination with nitrous acid at a pH value of 3.9. Methods (a) and (b) are described in the examples.

The active fragments are characterised in that they contain from 14 to 18 sugar units. Structural analysis shows the same main structural components as in standard heparin, i.e. L-iduronosyl-2-O-sulphate-(1α-4)-N-sulpho-D-glucosamine-6-O-sulphate as the dominating saccharide unit. However, the amount of unsulphated iduronic acid is considerably higher than in the starting material. Periodate oxidation has shown that the component takes a definite position in the molecule situated from 3 to 5 sugar units counted from the unreducing terminal. The active fragments have the structure (U-G)$_n$-I-G-(U-G)$_m$ where n is 1 or 2 and m is 5 or 6, I is unsulphated L-iduronic acid, U is L-iduronic acid-2-O-sulphate and G is N-sulpho-D-glucosamine-6-O-sulphate. A few U units may lack O-sulphate or be replaced by D-glucuronic acid and, similarly, a few G units may lack O-sulphate or be replaced by N-acetyl-D-glucosamine units. Reducing or unreducing terminal units may vary with the type of method of preparation used; thus e.g., deaminitive splitting of heparin leads to the formation of 2,5-anhydro-D-mannose in reducing terminal position. The active fragments may be characterised by means of physico-chemical methods, such as determination of mobility in an electric field and UV, IR and NMR spectra. However, the numerical values obtained do not give complete information, as also coagulation-inactive fragments substantially show similar characteristics. This depends on the fact that the biologic activity is derived from a specific sequence of the sugar residues where the position of the unsulphated uronic acid is especially important. Thus, only a gross

composition and size does not warrant that the component is active.

The invention is further illustrated by the following examples.

EXAMPLE 1

Preparation of heparin fragments by depolymerisation of standard heparin with nitrous acid

Heparin (0.5 g) isolated from swine intestines and dissolved in 150 ml of water is chilled to +40° C. and brought to pass through a 3×7 cm column of Dowex ®50 W-28 (H^+ form), 200–400 mesh. The column is then washed with 100 ml of water and the washing liquid is combined with the sample. To the sample there are added 250 ml of dimethoxyethane (glyme) chilled to −20° C. and 10 ml of isoamyl nitrite and the mixture having a temperature of about −10° C. is allowed to stand for two minutes. The reaction is then discontinued by the addition of 10 ml of 10% Na^+-acetate. After addition of 5.2 liters of ethanol precipitated carbohydrate (heparin derivatives) is recovered by centrifugation. The product is dissolved in 500 ml of 0.05M NaCl - 0.05M Tris-HCl, pH 7.4. This solution is fractionated, divided into 100 ml portions, by affinity chromatography on a column containing 75 ml of anti-thrombin-agarose-Sepharose ® (Pharacia Fine Chemicals, Uppsala, Sweden) (about 5 mg of protein per ml gel). The column is eluated by a salt gradient (500 ml of 0.05M NaCl-0.05M Tris-HCl in the mixing vessel; 500 ml of 3M NaCl-0.05M Tris-HCl in the reservoir), the major part of the applied material either passing unretardedly through the column or being eluated at a low ion strength (less than 0.4M NaCl); this material has no biologic activity. The active components (purified heparin derivatives) are eluated in a wide top between 0.05M NaCl and 3M NaCl corresponding to about 4% of the starting material. These fractions are pooled and desalted by gel chromatography.

Heparin derivatives prepared and purified in said manner have a molecular size corresponding to that of a tetradeca-octadecasaccharide (molecular weight 3600–4800). Structural analysis show the same structural components as in the starting material, L-iduronosyl-2-O-sulphate-(1α-4)-N-sulpho-D-glucosamine-6-O-sulphate being the dominating disaccharide unit. However, the amount of unsulphated iduronic acid has increased from about 6% in the starting material to about 16%. As to other aspects the structure agrees with the above description.

Example 2

Partial depolymerisation of heparin or heparin by-product by periodate oxidation at a pH value of 3° and 4° C. and subsequent alkali-treatment and reduction

Under these conditions the polysaccharide chain is split at D-glucuronic acid units resulting in only moderate loss of anticoagulation activity (Fransson and Lewis, FEBS Letters, 1979, in press). Standard Heparin (0.5 g) is dissolved in 250 ml of a solution (4° C.) containing 0.02M $NaIO_4$, 0.2M $NaClO_4$ and 0.05M Na^+-citrate buffer, pH 3.0. After three hours incubation in dark at +4° C. the oxidation is discontinued by the addition of a molar excess of D-mannitol and, then, the solution is dialysed and freeze-dried. Splitting of the polysaccharide chains at oxidised D-glucuronic acid units is effected by treament of the product with alkali (5 mg/ml of aqueous solution adjusted to pH 12 with 1M NaOH) at room temperature. After ten minutes the solution is neutralised with 1M acetic acid and, then, the material is desalted by gel chromatography on dextran material (Sephadex ® G-25, Pharmacia Fine Chemicals, Uppsala, Sweden). The product obtained can be reduced with sodium borohydride.

Heparin treated in said manner is considerably depolymerised compare to the starting material; gel chromatography shows that the resulting fragments have a size corresponding to 10–25 sugar units and, therefore, they ae somewhat larger than the fragments isolated after treatment with nitrous acid according to Example 1. Totally about 20% of the uronic acids in the polysaccharide are destroyed under the periodate oxidation (pH 3, 4° C., 3–6 hours). Purification by affinity chromatography of the oxidation products on antithrombinagarose-Sepharose ® gave a yield of about 30% of high-affinity material after three hours and a yield of 15% after six hours oxidation. The products thus obtained had an antifactor X_a-potentiating effect determined according to Example B in plasma of more than 1000 units/mg compared to 3rd International Heparin Standard.

Studies on anticoagulation activity

The heparin fragment prepared according to Example 1 was studied in view of its capacity to: (A) accelerate the inhibition of the coagulation enzyme thrombin; (B) accelerate the inhibition of activated coagulation factor X; (C) prolong the coagulation time in the blood plasma coagulation test APTT (Activated Partial Thromboplastine Time); (D) be neutralised by blood plasma components; and (E) influence the aggregation of thrombocytes.

EXAMPLE A

Inhibition of thrombin

The capacity of the heparin fragment to potentiate the inhibition of thrombin with antithrombin III was analysed according to a modification of a method by Teien et al. (Thrombosis Research 11, p. 107–117, 1977). The heparin fragment was found to have a specific activity of less than 20 E/mg compared to 120–170 E/mg for standard heparin.

EXAMPLE B

Inhibition of activated factor X

The capacity of the heparin fragment to potentiate the inhibition of activated factor X in plasma and in pure antithrombin III was studied according to a modified version of a method by Teien et al. (Thrombosis Research 8, 413, 1976). The heparin fraction was shown to have a specific activity of 500 E/mg in a pure antithrombin III system and 2100 E/mg in a plasma system compared to 120–170 E/mg for standard heparin.

EXAMPLE C

Prolongation of the coagulation time

The capacity to prolong the coagulation time of blood plasma was studied according to the APTT (Activated Partial Thromboplastine Time) method [Andersson et al., Thromb. Res. 9, 575 (1976)]. The heparin fragment showed a specific activity of less than 20 E/mg compared to 3rd International Heparin Standard. Standard heparin shows a specific activity in the range 120–170 E/mg.

EXAMPLE D

Neutralisation of heparin fragments in blood plasma

The heparin-neutralising effect of plasma components was studied by measuring the effect of heparin and the heparin fragment in plasma and in a pure antithrombin system. This was performed by measuring the amount of activated factor X inhibited in the two systems in the presence of a certain amount of heparin or heparin fragment. The activity of the heparin fragment showed a 15% neutralisation by plasma components, while the corresponding value of standard heparin was shown to be 75%.

EXAMPLE E

Thrombocyte influence

The capacity of the heparin fragment to aggregate thrombocytes at critical ADP (Adenosine DiPhosphate) concentrations was substantially studied according to Beck, E. A. (Thromb Haem Stuttg. 1977, **38**, 578). It was shown that the thrombocyte-aggregating capacity of the heparin fragment was ten times lower than that of standard heparin, calculated on the weight.

The heparin fragment according to the invention is incorporated into pharmaceutical preparations for clinical use, preferably in aqueous solution for injection or in ointment preparations for administration via the skin and mucous membranes.

We claim:

1. Heparin fragments having 14–18 sugar units, wherein the main component is the disaccharide unit L-iduronosyl-2-O-sulphate-N-sulpho-D-glucosamine-6-O-sulphate, and where unsulphated L-iduronic acid is in a position situated 3–5 sugar units from the unreducing terminal and is followed by a unit selected from the group consisting of N-sulpho-D-glucosamine sulphate and N-acetyl-glucosamine in sulphated and unsulphated form.

2. Heparin fragments having the structure $(U\text{-}G)_n\text{-}I\text{-}G\text{-}(U\text{-}G)_m$ where n is 1 or 2 and m is 5 or 6, I is unsulphated L-iduronic acid, U is L-iduronic acid-2-O-sulphate, and G is N-sulpho-D-glucosamine-6-O-sulphate.

3. Pharmaceutical compositions for preventative treatment or treatment of arterial thrombosis containing heparin fragments having selective anticoagulation activity and containing 14–18 sugar units, wherein the main component is the disaccharide unit L-iduronosyl-2-O-sulphate-N-sulpho-D-glucosamine-6-O-sulphate, and where unsulphated L-iduronic acid is in a position situated 3–5 sugar units from the unreducing terminal and is followed by a unit selected from the group consisting of N-sulpho-D-glucosamine sulphate and N-acetyl-glucosamine in sulphated and unsulphated form in an amount sufficient for anticoagulation activity; and a pharmaceutical carrier.

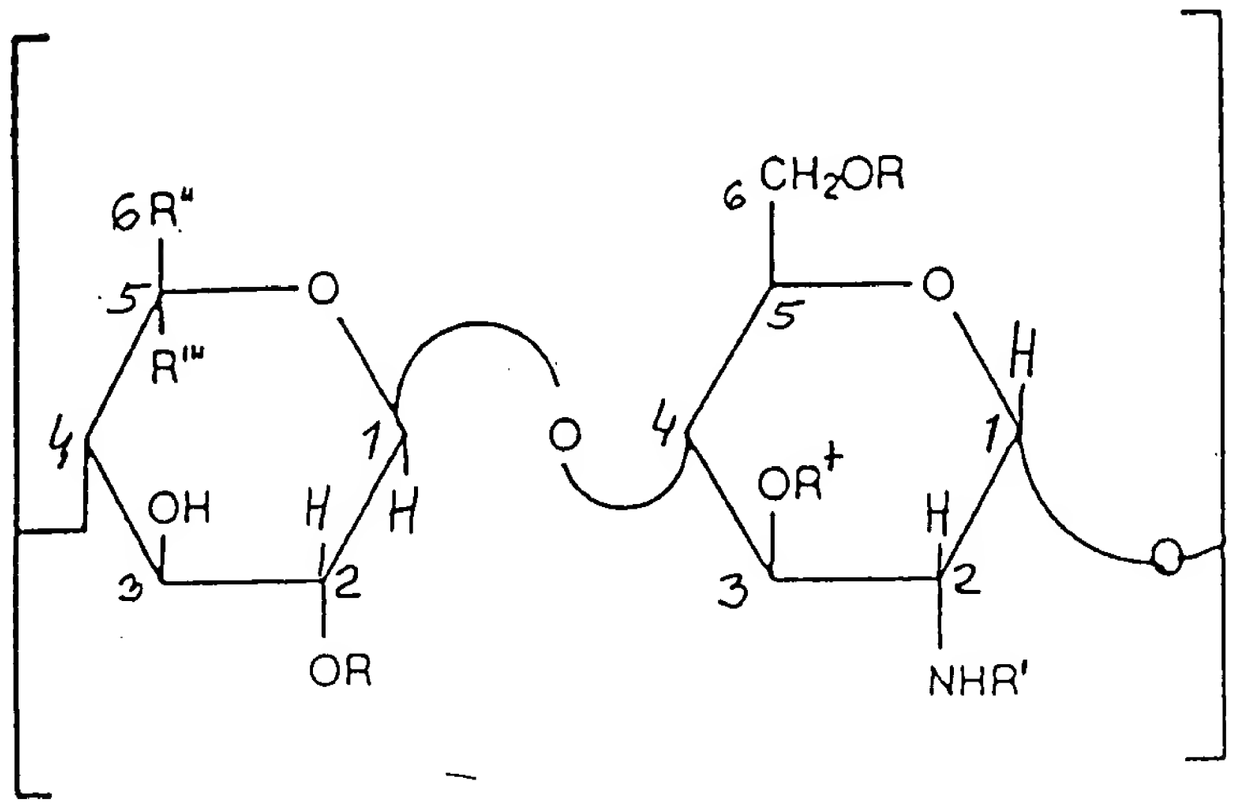
4. Pharmaceutical composition for preventative treatment or treatment of arterial thrombosis containing heparin fragments of the structure $(U\text{-}G)_n\text{-}I\text{-}G\text{-}(U\text{-}G)_m$ where n is 1 or 2 and m is 5 or 6, I is unsulphated L-iduronic acid, U is L-iduronic acid-2-O-sulphate and G is N-sulpho-D-glucosamine-6-O-sulphate in an amount sufficient for anticoagulation activity; and a pharmaceutical carrier.

5. The composition of claim **3** or **4** wherein said carrier is water.

6. The composition of claim **3** or **4** which is in the form of an ointment.

* * * * *

Structural formula



R = SO_3Na

R' = SO_3Na

R'' = H R''' = COONa

$R^+ = H$

n = 3-20

Exhibit 4

^{1}H NMR SPECTRUM OF FRAGMIN 52454

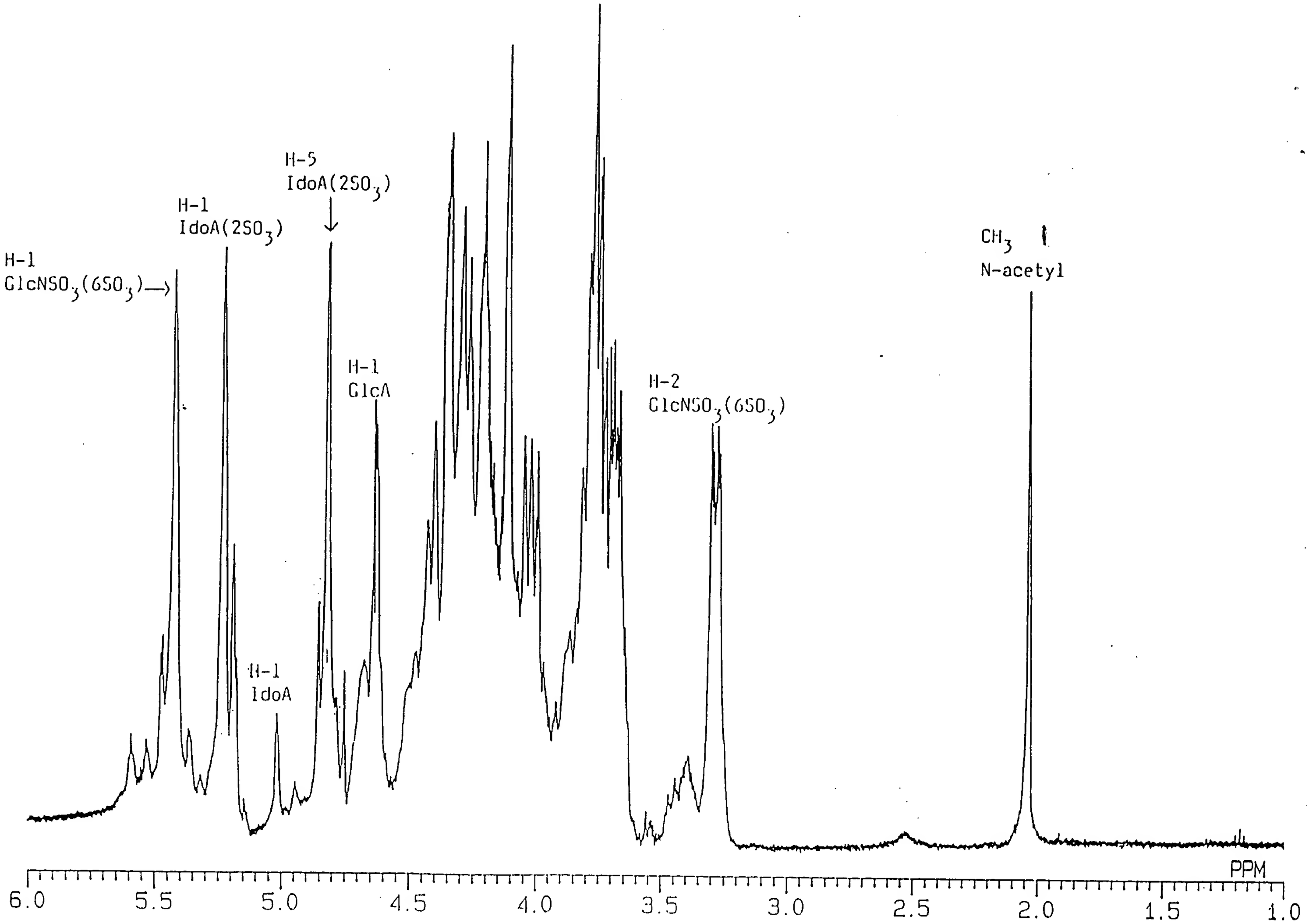


Exhibit 5

Exhibit 6

R & R REGISTRATIONS
P.O. Box 262069 • San Diego, California 92196 - 2069
PHONE/FAX (619) 586-0751

Ronald G. Leonardi, Ph.D., President

NDA 20-287
FRAGMIN®, Dalteparin sodium

August 06, 1992

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

RE: Original New Drug Application for Fragmin®.

Dear Ladies and Gentlemen:

Pursuant to Title 21 of the Code of Federal Regulations part 314.50 Kabi Pharmacia, AB, Uppsala, Sweden is here by submitting, in duplicate, an original New Drug Application for Fragmin®, Dalteparin sodium.

As noted in the full prescribing information we are seeking the approval of Fragmin for use as prophylaxis against thromboembolic complications in the intra- and postoperative surgical period. Specifically, FRAGMIN® is indicated for prophylaxis against deep venous thrombosis and pulmonary embolism in patients with a risk of thromboembolic complications associated with surgery.

This submission consist of 93 volumes, 1.1 to 1.93. In Volume 1.1 we have included all information required for the Index and Summary sections of the NDA. This includes the Table of Contents for the entire NDA, the Annotated Package Insert as well as Patent information. Volumes 1.2 to 1.4 consist of Chemistry, Manufacturing and Control information and contains a properly executed Environmental Assessment analysis. Volumes 1.5 and 1.6 contain the Methods Validation package while Volumes 1.7 to 1.10 describe the Non-Clinical Pharmacology and Toxicology section. The Human Pharmacokinetic and Bioavailability section is contained in Volumes 1.11 to 1.13 and is a repetition of the Clinical Pharmacology section.

The clinical program for Fragmin is as follows:

A. Pharmacokinetic and Pharmacodynamic Studies (14 studies designated with a C prefix; Volumes 1.14, 1.15, 1.16)

B. Controlled Thromboprophylaxis Studies (16 studies designated with a D prefix; Volumes 1.17 to 1.47)

C. Uncontrolled Thromboprophylaxis Studies (11 studies designated with an E prefix; Volumes 1.48 to 1.52.

R & R REGISTRATIONS

NDA 20-287
FRAGMIN®, Dalteparin sodium

August 06, 1992
Original, New Drug Application

D. Other Studies (22 studies designated with an F prefix; Volumes 1.53 to 1.55) and additional Information (Volumes 1.56 to 1.57; On-going clinical trials, experience in countries where Fragmin is now marketed, package insert in those countries, and reference to the literature).

Volumes 1.58 and 1.59 contain the information and documentation for the Integrated Effectiveness, Safety and Benefits/Risks data.

The statistical section is a repetition of the pivotal trials of the clinical section and is contained in Volumes 1.60 to 1.87.

Because we have included case report tabulations in the individual clinical reports we have not created a separate section. All the data and information is contained in the clinical reports. We have included the Case Report Forms for the deaths and drop outs in Volumes 1.88 to 1.93. This the entire contents of NDA 20-287 for Fragmin, Dalteparin sodium.

Also, please find enclosed a completed and signed Form FDA 356H along with attached Patent information. This information is also inclosed in Volume 1.1, pages 006 to 008.

Further, Kabi Pharmacia certifies that we did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) in connection with this application.

Kabi Pharmacia is prepared to discuss the contents of this submission to assist and expedite Agency review. Should this be necessary, or should any questions arise during your evaluation of this NDA, please contact Mr. Karl Posselt of Kabi Pharmacia Inc., 800 Centennial Avenue, Piscataway, NJ. 08855, phone number is 908-457-8143.

Sincerely,

Ronald G. Leonardi, Ph. D.
President
R & R REGISTRATIONS

Exhibit 7

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-287

Kabi Pharmacia, AB
Attention: Mr. Ronald Posselt
800 Centennial Avenue
Piscataway, New Jersey 08855-1327

AUG 1 1 1992

Dear Mr. Posselt:

We have received your new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Fragmin (dalteparin sodium injection)

Date of Application: August 6, 1992

Date of Receipt: August 7, 1992

Our Reference Number: NDA 20-287

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)(1) of the Act on October 6, 1992 in accordance with 21 CFR 314.101(a).

If the application is filed, the due date is February 3, 1993.

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDB 4820.6, you may request an informal conference with this division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Bronwyn Collier

Bronwyn Collier
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Exhibit 8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-287

SEP 25 1992

Kabi Pharmacia, AB
Attention: Mr. Karl Posselt
800 Centennial Avenue
Piscataway, New Jersey 08855-1327

Dear Mr. Posselt:

Please refer to your August 6, 1992 new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Fragmin (dalteparin sodium injection).

We have given your NDA a preliminary review, and we find it is not sufficiently complete to merit a critical medical and technical review. Thus, it will not be filed as a new drug application within the meaning of section 505(b)(1) of the Act.

We are refusing to file this NDA under 21 CFR 314.101(d) for the following reasons:

Clinical/Statistical

1. Information regarding the applicability of the clinical data to the U.S. population and U.S. medical practice as required under 21 CFR 314.106 (b) could not be located.

2. The reasons patients were dropped from studies D-1 and D-4 and an explanation of how study dropouts were replaced could not be located.

3. In study D-1, positive leg scans were to be verified by venography. An explanation for the absence of venography results in seven of the patients with positive leg scans in the placebo treatment group could not be located.

Biopharmaceutics

4. Validation for the assay method for anti-Xa activity used in the pharmacodynamic studies could not be located.

Chemistry/Manufacturing/Controls

5. The Environmental Assessment does not meet the regulation for addressing the environmental effects abroad (21 CFR 25.50). A statement of compliance to German law from the appropriate German authority would be acceptable.

Administrative

6. Translation of all foreign language material was not provided. Examples include, but are not limited to, Vol 1.2 pgs 65-70, Vol 1.56 pgs 287 337, 193, 200, and 358.

While not filing issues, the following scientific questions should be addressed in the NDA:

Clinical/Statistical

1. Please provide the following information regarding study randomization for pivotal trials D-1, D-4, and D-8:

   a. The pre-established randomization list generated using random number sequence(s) and the actual treatment assignments given.

   b. An explanation for any deviations from the pre-established randomization list that may have occurred.

   c. The random number sequences used for treatment assignments.

2. If possible, please provide the following information on diskette:

   a. Study summaries (Word Perfect 5.1 or ASCII) and data tables (ASCII) for the pharmacodynamic studies.

   b. Efficacy and demographic data preferably on SAS data sets for each pivotal trial including identifying codes for treatments, patients, centers and evaluable patients and dropouts with revisions.

Biopharmaceutics

3. Please provide quality control information for the anti-Xa assay used in each pharmacodynamic study.

4. Please provide available pharmacodynamic information regarding Fragmin administration in hepatically impaired patients.

Chemistry/Manufacturing/Controls

5. Please specify whether the proposed market product is identical to drug used in clinical trials, i.e. no changes in formulation, manufacturing method, or raw material suppliers. If there are differences, please provide a history of the differences and where they occured.

6. The manufacturing method for Fragmin must include animal source (including country of origin) and organ, manufacturing methods for crude and purified heparin, and the complete heparin specifications and test methods from each supply source. Each heparin manufacturing method is considered to be unique and will result in a different method of manufacture of Fragmin drug substance. The stability data for the drug substance and drug product must be related to commercial size production and must support the use of each heparin supplier.

7. Please describe the method for relating the source of heparin raw material to each finished batch of drug product.

8. Please identify the largest commerical scale of Fragmin production you intend to produce and the largest batch produced to date. Please list any changes you intend to make for scale-up in production size.

9. Please provide a classification list, as to their intended purpose, of all the documents furnished for the chemistry, manufacturing and controls for Fragmin, e.g. technical support, validation, pharmaceutical development, developmental analytical, actual test method or assay for a specification, etc.

10. Please provide a master production record or a completed batch record for the manufacture of the drug product. This should include a complete description of the process for holding the sterile filtered solutions at 2-8^{0}C prior to filling and the methods for maintaining their sterility.

Preclinical Pharmacology

11. Preclinical studies evaluating the hemolytic and protein precipitating properties of Fragmin should be provided.

12. Information on the sensitization potential of Fragmin should be provided.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference. If you have any questions please call:

Bronwyn Collier
Consumer Safety Officer
(301) 443-0487

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference.

Sincerely yours,

Stephen Fredd M.D.

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Exhibit 9

Kabi Pharmacia

December 22, 1992

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Gastrointestinal and Coagulation Drug Products
HFD-180
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-287
Fragmin® (dalteparin sodium injection)

Gentlemen,

Reference is made to your letter of September 25, 1992 describing six reasons for refusing to file the above application.

We are submitting herewith archival and review copies containing documentation which addresses these refusal to file issues. The remaining issues described in your letter are under review and will be responded to in a separate submission.

Please contact me at (908) 457-8143, should there be any questions concerning the enclosed documentation.

Very truly yours,

Karl C. Posselt

Karl A. Posselt
Director of Regulatory Compliance

KAP:rs

CC/Letter Only: A.P. Wiklund
J.A. Nitche
M. Lundberg

CC/Full Submission: K. Byrstrom

Kabi Pharmacia
800 Centennial Avenue
Piscataway, NJ 08855-1327

Telephone
Telex

Exhibit 10

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-287

Kabi Pharmacia AB
Attention: Mr. Karl A. Posselt
800 Centennial Avenue
Piscataway, New Jersey 08855-1327

JAN 12 1993

Dear Mr. Posselt:

We have received your new drug application resubmitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Fragmin (Dalteparin Sodium) Injection

Date of Application: December 22, 1992

Date of Receipt: December 30, 1992

Our Reference Number: NDA 20-287

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)(1) of the Act on February 28, 1993 in accordance with 21 CFR 314.101(a).

If the application is filed, the new due date is June 29, 1993.

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDB 4820.6, you may request an informal conference with this division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0437.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Bronwyn Collier

Bronwyn Collier
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
HFD-180

RECEIVED
JAN 14 1993

Exhibit 11

BRKA 94-12-15

Request and application for extension of patent term

IND - Investigational New drug application

March 1, 1985 Submitted application to FDA
March 14, 1985 FDA letter acknowledging receipt of Pharmacia's application and assigned it number 25,924

Note: This IND was submitted without presentation of a clinical trial protocol under the IND. There was not any clinical trial performed under the IND, that was reported as a base for our claim in the NDA

HISTORICAL REVIEW

85-03-01	PAB	submits IND and asks for pre-NDAmeeting	
85-03-14	FDA	assigns IND 25,924	
86-05-19	FDA	questions re IND.	
86-06-30	PAB	letter re compassionate use/Dr Hochberg	
86-07-07	PAB	letter re compassionate use/Dr Merli	
86-07-21	PAB	call re compassionate use/Dr Merli, 2nd patient	
87-02-18	PAB	subm. study protocol, oral absorbt/Dr Björnsson	
87-03-18	PAB	subm. response to FDA questions of 86-05-19.	
87-05-08	PAB	subm. Annual progress report	
88-06-15	PAB	subm. Annual progress report	ser 001
89-01-27	PAB	subm.Inform amendm/Chemistry	Ser 002
89-02-03	PAB	subm amendm/new prot&invest,NIH	Ser.003
89-03-29	FDA	answer to amendm(Ser.002)&requests	
89-05-08	PAB	subm.Inform amendm/CMC syringes	Ser.004
89-07-25	PAB	subm. Annual report	Ser.005
89-09-11	PAB	response to FDA request 89-03-29	Ser.006
90-01-05	FDA	answer to amendm/CMC doc(87-03-18,89-01-27, 89-05-08,pre-NDApack 89-11-01;15;27)&requests	
90-02-08	FDA	call re mistake in nrs of questions in Jan 5 letter	
90-04-26	PAB	letter re CMC issues.	
90-05-21	PAB	subm amendm/compass/Dr.Hochberg, ser 007	
90-06-29	PAB	subm IRB appr re ser 007	
90-07-16	PAB	submits Annual progress report	ser 008
91-09-25	FDA	requests Annual progress report	
91-10-08	PAB	subm. Annual progress report, close of NIH-study.	ser 009
92-01-31	PAB	subm amend/new prot&invest DVTx1;91-030	ser 010
92-03-17	PAB	subm amendm/new prot&invest HIP91-137	ser 012

NDA - New Drug Application

Pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic act; and 21 CFR 314.50 for Fragmin (dalteparin sodium injection)

August 6, 1992	Submitted the New Drug Application for use as prophylaxis against thromboembolic complications in the intra- and postoperative surgical period.
August 11,1992	FDA acknowiedging receipt of Pharmacia's application and assigned it Reference nr: NDA 20 -287
September 25, 1992	FDA refusal to file letter.
December 22, 1992	Pharm.resubmits NDA(address.the refusal to file)
December 30, 1992	FDA acknowledges receipt of December 22 letter
February 28, 1993	Official date of the submission of a new drug application under section 505(b)(1) of the FD&C ACT in accordance with 21 CFR 314.101(a)

HISTORICAL REVIEW

First year:

85-03-01	PAB	submits IND and asks for pre-NDA meeting
85-04-16		Pre-NDA meeting, clin program for haemodialysis

Second- fourth year:IND activities only

Fifth year:

89-07-19	PAB	requests for pre-NDA submission meeting
89-08-11	PAB	requests for pre-NDA submission meeting, 2nd time as previous letter of 89-07-19 got lost at FDA
89-09-19	PBA	submits desk copies for pre NDA meeting
89-09-29	FDA	pre-NDA meeting
89-11-02	FDA	sends summary of the pre-NDA meeting 89-09-29
89-11-01	FDA	call re CMC pre-NDA package.
89-11-15	FDA	"
89-11-27	FDA	"
89-11-28	PAB	submits company's summary of the pre-NDA meet.

Sixth year:

90-01-05	FDA	sends recomm/requests CMC pre-NDA package
90-02-08	FDA	call re mistake in nrs of Jan 5 letter
90-04-26	PAB	letter re CMC issues of Jan 5 letter
90-05-30	FDA	pre-NDA meeting re CMC in letter 90-01-05

90-07-10	PAB	submits comp's summary of 90-05-30 meeting
90-10-25	PAB	subm 3 cl.trial rpts/NDA format,asks pre-NDA meet
Seventh year:		
91-01-08	PAB	confirms date for pre-NDA submission meeting
91-01-21	PAB	confirms new date for pre-NDA subm.meeting
91-02-07		Pre-NDA submission meeting re 90-10-25 subm
91-05-18	PAB	submits company's summary of the pre-NDA meet.
91-09-04	FDA	sends summary of the pre-NDA meeting 91-02-07
Eigth year:		
92-08-06	PAB	submits NDA
92-08-11	FDA	assigns Ref.nr 20-287
92-09-25	FDA	sends RTF letter, 6 filing issues and 12 non-filing iss.
92-10-05	PAB	acknowl. RTF letter.
92-12-22	PAB	resubm NDA (addressing RTF 6 issues)
Ninth year:		
93-01-12	FDA	acknowl. receipt of resubmission
93-01-12	PAB	subm amendm to 92-12-22 letter
93-02-02	FDA	call re clarification preclin pharmacol in RTF letter
93-02-03	FDA	call re request for drug substance stability
93-02-03	FDA	call to advise NF items 4, 2a,2b in RTFletter
93-02-09	FDA	call to clarify NF items 11,12 in RTF letter
93-02-17	PAB	subm diskettes with statist.data NF item 2.b RTF
93-02-28		Date for official submission
93-03-02	PAB	call, FDA has 2 add stability req. on diskettes
93-03-12	PAB	subm responses to NFquest in RTF letter
93-03-12	PAB	subm answers on stability re FDA's call 93-02-03
93-03-16	FDA	call re inspection of clin trial sites D-1,D-2,D-4,D-5
93-03-22	FDA	call D-2 on hold
93-03-23	PAB	asks for review status conference
93-04-05	FDA	call stability diskettes not requested any more
93-04-05	FDA	call re review status conference not necessary
93-05-(18-23)	FDA	pre-approval inspection at Vetter in Germany
93-05-21	FDA	recommend and requests re CMCsect of NDA
93-06-01	FDA	call to request inf re NDA Summary of safety data
93-06-07	FDA	letter to Hepar request for add information
93-06-07	PAB	sends letter of assurance for FDA audits of D-1,D-4,D-5 studies re 93-03-16 FDA call
93-06-07	PAB	letter re Study D-4 and D-5/ audits
93-06-08	FDA	call re add inf on NDA Summary of safety data
93-06-09	PAB	letter providing add info on D-4 and D-10 audits
93-06-11	PAB	subm clin amendment re study D-10
93-06-15	PAB	letter re study D-1/audit
93-06-21	FDA	call re amendment to one DMF
93-06-(21-25)		audit Copenhagen study D-4, Törholm
93-06-22	PAB	subm requested AE frequency tables acc 93-06-08

93-06-24	FDA	inform review extended 60 days to August 28 because of 93-06-11 amendment for study D-10
93-06-24	PAB	subm corrected DMFnr request in 93-05-21 letter
93-06-25	FDA	call to disregard their 93-06-21 call.Stab data req. for it.4.A FDA letter 93-05-21
93-07-08	FDA	call and received inf re debarm. certif. in NDA
93-07-09	FDA	call to request inf for New Zealand D-1 audit
93-07-13	FDA	call to request add clin inf re dose select.
93-07-19	PAB	subm request A.E. freq. tables (any bleed compl)
93-07-(26-30)		audit in New Zealand D-1 (Ockelford)
93-06-(28 -07-01)		audit in Gothenburg study D-10 (Eriksson B)
93-08-03	FDA	call to remind about the request for dosage rational and appr.foreign labels
		For the latter reference was made to the NDAfile
93-08-11	PAB	subm answer for rational for dosag.93-07-13 call
93-08-18	FDA	call regarding typo in (D-8)93-08-11 letter
93-08-19	FDA	inform review extended 60 days to October 27 because of PAB 93-08-11 answer
93-08-24	FDA	letter request upd of safety information incl Bergq III
93-08-27	FDA	call re NIBSC standard for anti-Xa
93-08-31	PAB	call re 93-08-18 and clarif of typo, answer re stand of FDA call 93-08-27
93-09-01	PAB	submits request docum.for D-1/audit July 26-30,1993
93-09-17	FDA	requests corrected tabulation for study D-4
93-09-23	FDA	pre-approval inspection Strängnäs
93-09-28	PAB	call re 93-09-17 letter discussing the contents
93-10-05	FDA	letter acknowledge receipt of letter 01-09-93
93-10-12	PAB	subm amendm re bioavail questions of May 21,1993
93-10-13	PAB	subm amendm tables Study D-4/ answer to17-09-93
93-10-14	PAB	subm correct tables for audit study D-1,July 26-30
93-10-28	PAB	subm corr tables of orig hemogl NDA data.
93-11-05	PAB	subm Safety upd/request in Aug 24-letter.
93-11-08	PAB	subm answers to CMCquestions of May 21,1993
93-11-22	FDA	due to answer 93-11-08 extend.review to 94-02-15

Tenth year:

94-01-10	FDA	sends approvable letter,requests answer in 10 days
94-01-14	PAB	answers 94-01-10 approvable letter
94-01-27	PAB	call re review status of safety upd,reinspection Vetter, Bergqvist 3
94-01-31	FDA	call follow up on 94-01-27 disc.clin review ended after receipt of safety update.
94-02-18	PAB	call re Nov 8-93 CMC subm- status;planned FDA-meeting
94-02-18	PAB	asks for FDA-meeting re malign,orth.ind.
94-02-22		inspection at Pharmacia Hepar, Inc., USA
94-03-08	PAB	call re status CMC quest and time for meeting
94-03-09	PAB	letter confirm meeting 15-03-94

94-03-15	FDA	meeting
94-03-17	FDA	subm questions re Nov.8-93 amendm
94-04-27	PAB	letter re inaccurate inf Heparin sources in PAB's 93-03-12 letter and req for meeting.
94-05-05	PAB	call re April 27 letter
94-05-(09-13)	FDA	pre-approval inspection at Vetter
94-05-17	PAB	subm amendm to quest in 05-05-94 tel.convers.
94-05-24	PAB	subm answer to item 11,12 in RTFletter-92.
94-05-26	FDA	call to request nr of patients in Bergquist 3 study
94-05-31	PAB	answ to 94-05-26 call re Bergquist study
94-06-01	PAB	subm inform request at pre-appr insp Vetter
94-06-01	FDA	call re Hep source
94-06-02	PAB	call respond to FDA call 94-06-01 re Hep source
94-06-03	FDA	call to cancel requested FDA meeting re CMC
94-06-09	PAB	call re follow up of Heparin source
94-06-21	FDA	call no add info request re Hep sources
94-06-24	PAB	amendm to resp. to 17-03-94 letter exc.pt2
94-07-07	PAB	call re status NDA review. No decis.re Hep source
94-07-22	PAB	call FIC-group re PAI Vetter and status
94-07-28	PAB	subm follow-up response re PAI at Vetter
94-08-31	FDA	letter conf satisf CMC resp to May 21-93, Jan.10 and March 17-94 letters, requests of meth valid. pack
94-09-06	PAB/FDA	tel.conv.conf pt 1&2 of Jan 10-94 letter OK
94-09-22	PAB	amendm (ref FDAJan 10 letter and PAB March 9-94 and March15-94 meeting) draft of prescr inf
94-09-30	PAB	subm final print labels & commits to provide valid reg.methods.
94-10-17	FDA	call to say labelling review starts;request final saf upd status of Hepar cGMP not OK
94-10-11	PAB	subm final print prescr inform
94-11-15	FDA	call re labelling, request safety upd subm
94-11-16	FDA	letter pack insert, labels
94-11-16	FDA	call re clearance of Hepar compliance
94-11-16	PAB	submits safety update
94-11-16	PAB	call re clarif of wording in labelling
94-11-18	FDA	call re storage wording on labels
94-11-29	FDA	request
94-11-30	PAB	call with re labelling FDA 94-11-16
94-12-05	FDA	call request all revised labels by Dec.7
94-12-06	FDA	answer to 94-11-30
94-12-08	FDA	call re request of clarif of prescr.inform
94-12-09	FDA	call re cancel their request of 94-12-08

EXHIBIT 12

ASSIGNMENT OF APPLICATION FOR PATENT

Name(s) and address(s) of inventor(s)

WHEREAS:
Ulf Per Fredrik Lindahl, Torgvägen 7, 752 46 Uppsala, Sweden,
Gudrun Elisabet Bäckström, Rundvägen 34, 740 50 Alunda, Sweden,
John Yngve Lennart Thunberg, Flogstavägen 47B, 752 63 Uppsala, Sweden,
Lars-Åke Fransson, Mårtensloosvägen 33, 223 67 Lund, Sweden,
Lars-Olov Andersson, Vårbroddvägen 36, 741 00 Knivsta, Sweden,
Erik Yngve Holmer, Svartviksvägen 19, 161 32 Bromma, Sweden,
Inga Helena Sandberg, Ryavägen 70, 191 47 Sollentuna, Sweden,
Ewa Gunilla Söderström, Odenvägen 52, 133 00 Saltsjöbaden, Sweden
(hereinafter referred to as ASSIGNOR), have invented and own a certain invention entitled:

Title of invention

HEPARIN FRAGMENTS HAVING SELECTIVE ANTICOAGULATION ACTIVITY

for which application for Letters Patent of the United States has been executed on even date herewith, and

WHEREAS:

Name and address of assignee

KABI AB, Lindhagensgatan 133, 112 87 Stockholm, Sweden

(hereinafter referred to as ASSIGNEE), is desirous of acquiring the entire interest in, to and under said invention and the United States Letters Patent to be obtained therefor;

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the full and exclusive right, title and interest to said invention and all Letters Patent of the United States to be obtained therefor on said application or any continuation, division, renewal, substitute or reissue thereof for the full term or terms for which the same may be granted.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent as may be known and accessible to ASSIGNOR and will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to ASSIGNEE or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain and enforce said application, said invention and said Letters Patent which may be necessary or desirable to carry out the purposes hereof.

IN WITNESS WHEREOF, have hereunto set hand and seal this 12th day of December, 1979

RECORDED
PATENT & TRADEMARK OFFICE
JAN 4 1980

Full name(s) of inventor(s)

Ulf Per Fredrik Lindahl

Gudrun Elisabet Bäckström

John Yngve Lennart Thunberg

Lars-Åke Fransson

Lars-Olov Andersson

Erik Yngve Holmer

Inga Helena Sandberg

Ewa Gunilla Söderström

Instruction sheet for assignment

Signing

All information, names of inventor(s) and assignee and title of invention, should be completed. The assignment should be signed by the inventor(s) at the same time as the declaration for the patent application is signed.

No witnessing or legalization is necessary. However, if this assignment is legalized then it will only be prima facie evidence of the execution of the assignment.

LP 767

EXHIBIT 13

PATENT NUMBER: 4303651 ISSUE DATE: 12/01/81
SERIAL NUMBER: 06/109936 FILING DATE: 01/04/80
TITLE: HEPARIN FRAGMENTS HAVING SELECTIVE ANTICOAGULATION ACTIVITY
APPLICANT: LINDAHL, ULF P. F. ; BACKSTROM, GUDRUN E.
THUNBERG, JOHN Y. L. ; FRANSSON, LARS-AKE ; ANDERSON, LAR
HOLMER, ERIK Y. ; SANDLBERG, INGA H. ; SODERSTROM, EWA G.

REEL: 6223 FRAME: 0645 DATE RECORDED: 08/10/92 NUMBER OF PAGES: 003
ASSIGNOR: KABI VITRUM AKTIEBOLAG
EXC DATE: 05/07/92
ASSIGNEE: KABI PHARMACIA AKTIEBOLAG
BRIEF: CHANGE OF NAME
EFFECTIVE ON 12/04/1990

PRESS XMIT FOR NEXT PAGE OR FOR A SPECIFIC PAGE
ENTER PAGE NUMBER (2 DIGITS MAX.), PRESS XMIT

RETURN ADDRESS: LAW OFFICES OF POLLOCK, VANDE
SANDE & PRIDDY
BURTON A. AMERNICK
1990 M ST., N.W., STE. 800
WASHINGTON, D.C. 20036-3425

NO MORE INFORMATION FOR THIS PATENT NUMBER

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AND PRESS XMIT TO GO BACK TO DESIRED PAGE

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LAW OFFICES
POLLOCK, VANDE SANDE & PRIDDY
SUITE 800
1990 M STREET, N. W.
P. O. BOX 19088
WASHINGTON, D. C. 20036-3425

PATENT AND TRADEMARK CAUSES

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GEORGE R. PETTIT
LOUIS WOO
THOMAS J. VANDE SANDE
ELZBIETA CHLOPECKI
DEAN E. CARLSON*
EDDY L. TEZAK
ERIC J. FRANKLIN*

*NOT ADMITTED TO D.C. BAR

July 30, 1992

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Attention: Assignment and Certification Services Division
Assignment Branch

Sir:

Attached hereto is an original of the Certificate of Registration of Name Change from Aktiebolaget Kabi to KabiVitrum Aktiebolag to Kabi Pharmacia Aktiebolag. Please record this change of name against the following patents:

U. S. Patent No. 4,303,651	Lindahl et al
U. S. Patent No. 4,944,659	Labbe et al
U. S. Patent No. 5,052,562	Petho

Check no. 6205 in the amount of $120.00 is attached in payment of the fees associated with this request. However should any additional fee be necessary, the Commissioner is hereby authorized to charge same or credit any overpayment associated with this communication to Deposit Account 22-0185. A duplicate of this sheet is attached for the Finance Branch, if necessary.

Respectfully submitted,

Date: July 30, 1992

Burton A. Amernick
Registration No. 24,852
Attorney for Applicant(s)

BAA:bd

PATENT- OCH REGISTRERINGSVERKET
BOLAGSAVDELNINGEN, 851 81 SUNDSVALL

NATIONAL PATENT AND REGISTRATION OFFICE
COMPANIES DEPARTMENT

CERTIFICATE OF REGISTRATION

Registration number: 556029-7094

Date of registration: 1931-01-26

Date of registration of current company name: 1990-12-04

Company name: Kabi Pharmacia Aktiebolag

Address: 751 82 UPPSALA

Registered office: Uppsala

Share capital: Sek 500 000 000

Board of Directors
321016-0028 Maud Inga Margret Eberson, (A), Valsbergs Gränd 4, 126 35 HÄGERSTEN
360627-3716 Jan Erland Ekberg, Karl Magnussons väg 32, 541 41 SKÖVDE
300202-1651 Hans Gösta Forsberg, Roburvägen 9, 181 33 LIDINGÖ
401226-8035 John Sören Gyll, Strandpromenaden 3, 131 50 SALTSJÖ-DUVNÄS
491010-1817 Joseph Jenadri, (A), Imatragatan 164, 164 78 KISTA
450820-2431 Rolf Allan Klasson, (U), 269 Barrington Drive, Bridgewater 08807, NEW JERSEY, USA
410828-7113 Bernt Erland Magnusson, Väringavägen 11, 182 63 DJURSHOLM
370828-0494 Erling Carl Jacob Norrby, Tykövägen 21, 181 61 LIDINGÖ
461008-4719 Gustav Lennart Persson, (A), Gevärsgatan 1, 262 62 ÄNGELHOLM
230224-1134 Knut Lennart Alf Åkerman, Box 76, 430 41 KULLAVIK
370624-1654 Kurt Ingemar Östlund, Caritasgatan 22 A, 216 18 MALMÖ

Deputy members of the Board
450401-4194 Nils Roland Håkansson, (A), Lokvägen 25 F, 260 33 PÅARP
430213-3527 Britta Kaul, (A), Drottning Kristinas väg 24, 193 00 SIGTUNA
331105-8204 Marianne Rindert, (A), Svedbovägen 50, 740 20 BRUNNA

The Managing Director is Jan Erland Ekberg and the Deputy Managing Director is:
470417-9193 Per Håkan Albin Åström, Edsviksvägen 69, 191 43 SOLLENTUNA.

Other persons authorized to sign on behalf of the company:
490414-1415 Lars Rolf Bosson Ingelmark, Skålleredsvägen 94, 439 00 ONSALA
411009-3913 Lars Ingvar Jeppsson, Tussilagovägen 12, 541 41 SKÖVDE
541123-0054 Mats Olof Magnus Lidgard, Djursholmsvägen 95, 183 51 TÄBY
370506-0337 Lars Gunnar Lindegren, Hummelvretsvägen 29, 178 00 EKERÖ
450703-7135 Nils Göran Pettersson, Östermalmsgatan 68 A, 114 50 STOCKHOLM
501002-1698 Nathanael Weitzberg, Torstenssonsgatan 8, 114 56 STOCKHOLM

Company auditor
400517-6211 Hans Gunnar Karlsson, Åsögatan 137, 4 tr, 116 24 STOCKHOLM

(contd.)

Besöksadress:
Bodhusparken

Telefon: vx 060-18 40 00
Postgiro: 95 06 08-0

Telefax: 060-12 64 77 adm
060-11 56 29 info

PATENT- OCH REGISTRERINGSVERKET

NATIONAL PATENT AND REGISTRATION OFFICE
COMPANIES DEPARTMENT

(contd.)

Registration number: 556029-7094

In addition to the Board of Directors, any two jointly of Ekberg, Gyll, Åström, Ingelmark, Jeppsson, Lidgard, Lindegren, Pettersson, and Weitzberg, are entitled to sign on behalf of the company.

Pursuant to Section 8, sub-section 12, of the Companies Act, the Managing Director, in his normal business activities, is also entitled to sign on behalf of the company.

Note: Since nine members and no deputy members have been stipulated for the Board of Directors, the board is incomplete.

Financial Year
Registered financial year: 0101-1231
Latest annual report submitted covers financial period 900101-901231.

Previous company names:
Kärn-bolaget aktiebolag, registered 1931-01-26
Aktiebolaget Kabi, registered 1951-03-30
KabiVitrum Aktiebolag, registered 1978-11-27

Sundsvall 1992-05-07
Ex officio

Maureen Sundin

PATENT-OCH REGISTRERINGSVERKET * PRV *

(A) = employee representative
(U) = citizen of foreign country or Swedish subject residing abroad

EXHIBIT 14

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DATE: 01/09/95
TO:

N09B
POLLOCK, VANDE SANDE & PRIDDY
BURTON A. AMERNICK, ESQUIRE
P.O. BOX 19088
1990 M STREET N.W. SUITE 800
WASHINGTON, D.C. 20036

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR: DOC DATE: 04/29/94
KABI PHARMACIA AB

RECORDATION DATE: 01/06/95 NUMBER OF PAGES 007 REEL/FRAME 7235/0329

DIGEST : MERGER (SEE DOCUMENT FOR DETAILS).

ASSIGNEE:
PHARMACIA AKTIEBOLAG
S-171 97 STOCKHOLM
STOCKHOLM, SWEDEN

SERIAL NUMBER 6-109936 FILING DATE 01/04/80
PATENT NUMBER 4,303,651 ISSUE DATE 12/01/81

EXAMINER/PARALEGAL
ASSIGNMENT BRANCH
ASSIGNMENT/CERTIFICATION SERVICES DIVISION

Patent and Trademark Office

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Kabi Pharmacia AB
Rapsgatan 7
S-751 82 Uppsala
SWEDEN

Additional party(ies) attached? No

2. Nature of Conveyance:

[ ] Assignment [X] Merger
[ ] Change of Name
[ ] Other _____

Execution Date: April 29, 1994

3. Name and address of receiving party(ies):

Name: PHARMACIA AKTIEBOLAG

Address: S-171 97 Stockholm
SWEDEN

Additional names & addresses? No

4. Application number(s) or patent number(s): 4,303,651

If this document is being filed together with a new application, the execution dates of the application are:

A. Patent Application No.(s) B. Patent No.(s)

Additional number attached? No

5. Party to whom correspondence concerning this document should be mailed:

Burton A. Amernick, Esquire
Pollock, Vande Sande & Priddy
P.O. Box 19088
1990 M Street, N.W. Suite 800
Washington, D.C. 20036

6. Total number of applications or patents involved: 1

7. Total Fee (37 CFR 3.41) $ 70.00
($40.00 Assignment Fee and $30.00 Expediting Fee)
xx Enclosed
_____ Charge to Deposit Account
xx Charge insufficient funds

8. Deposit account No.: 22-0185

9. Statement and signature

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Burton A. Amernick		January 6, 1995
Name of person signing	Signature	Date

Total number of pages, including cover sheet, attachments and document: 7

Mail documents to be recorded with required cover sheet information to:

Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

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I certify that the attached is a true copy of the Certificate of Registration of the Merger of Kabi Pharmacia to Pharmacia Aktiebolag.

Date: January 6, 1995

BURTON A. AMERNICK (Reg 24852)

PATENT- OCH REGISTRERINGSVERKET
BOLAGSAVDELNINGEN, 851 81 SUNDSVALL

CERTIFICATE OF REGISTRATION

Registration number: 556131-9608

Date of registration: 1969-12-30

Company name: Pharmacia Aktiebolag

Address:

Registered office: 171 97 STOCKHOLM
Stockholm

Share capital: SEK 6.340.955.550

BOARD OF DIRECTORS:
440923-1471 Augustsson, Kurt Artur, (U), Beddingen 2, 0250 OSLO 2, Norge
380303-0497 Douglas, Gustaf Archibald Siegwart, Rydboholms gård, 184 92 ÅKERSBERGA
360627-3716 Ekberg, Jan Erland, Norregatan 12, 296 00 ÅHUS
300202-1651 Forsberg, Hans Gösta, Roburvägen 9, 181 33 LIDINGÖ
401226-8035 Gyll, John Sören, Strandpromenaden 3, 131 50 SALTSJÖ-DUVNÄS
491010-1817 Jenadri, Joseph, (A), Imatragatan 164, 164 78 KISTA
301022-0014 Lund, Olof Gösta, Zetheliusvägen 1, 644 00 TORSHÄLLA
340202-5013 Mannheimer, Carl Sören, Berggrensgatan 14 B, 412 73 GÖTEBORG
371114-0669 Olivero-Reinius, Ulla Birgitta, Sibyllegatan 61, 114 43 STOCKHOLM
340521-4655 Samuelsson, Bengt Ingemar, Framnäsvägen 6, 182 63 DJURSHOLM
440422-0511 Tegnér, Per Axel Arne, Söderliden 7, 181 60 LIDINGÖ
300610 von Hertzen, Gustav, (U), Skarpskyttegatan 3 B 22, SF00130, HELSINGFORS, FINLAND

DEPUTY MEMBERS OF THE BOARD:
340825-2710 Hammarström, Bo Åke Melik, (A), Starvägen 3, 756 52 UPPSALA
491214-0326 Sander, Ingela Elisabet, (A), Skorpvägen 20, 161 71 BROMMA

MANAGING DIRECTOR:
360627-3716 Ekberg, Jan Erland, Norregatan 12, 296 00 ÅHUS

DEPUTY MANAGING DIRECTOR:
390318-8930 Blomberg, Jan Fredrik, Furusundsgatan 12, 8 tr, 115 37 STOCKHOLM

OTHER PERSONS AUTHORIZED TO SIGN ON BEHALF OF THE COMPANY:
520425-0038 Blomberg, Nils Carl-Johan, Jägarstigen 73, 181 46 LIDINGÖ
321017-6834 Borg, Rune Helmer, Holmgårdsvägen 4, 193 00 SIGTUNA
510119-3356 Carlson, Hans William, Lärkvägen 9, 183 51 TÄBY
490414-1415 Ingelmark, Lars Rolf Bosson, Skälleredsvägen 94,

CONTD.

PATENT- OCH REGISTRERINGSVERKET
BOLAGSAVDELNINGEN, 851 81 SUNDSVALL

CERTIFICATE OF REGISTRATION

Registration number: 556131-9608

Date of registration: 1969-12-30

Company name: Pharmacia Aktiebolag

Address:
171 97 STOCKHOLM
Registered office: Stockholm

Share capital: SEK 6.340.955.550

439 32 ONSALA
411009-3913 Jeppsson, Lars Ingvar, Tussilagovägen 12,
541 41 SKÖVDE
541123-0054 Lidgard, Mats Olof Magnus, Djursholmsvägen 95,
183 51 TÄBY
470417-9193 Åström, Per Håkan Albin, Edsviksvägen 69 B,
191 43 SOLLENTUNA

COMPANY AUDITORS:
400517-6211 Karlsson, Hans Gunnar, Åsögatan 137. 4 tr,
116 24 STOCKHOLM
460515-0657 Tidström, Hans Göran, Knut Wallenbergs väg 39,
133 00 SALTSJÖBADEN

DEPUTY AUDITORS:
470411-7219 Danielsson, Åke Nils Gunnar, Neptunistigen 70,
162 40 VÄLLINGBY
451120-7732 Holm, Peter Axel Anders, Vinbärsvägen 16,
133 00 SALTSJÖBADEN

SIGNATORY POWER:
In addition to the Board of Directors,
Ekberg, Jan Erland
alone,
or any two jointly of
Blomberg, Jan Fredrik
Blomberg, Nils Carl-Johan
Borg, Rune Helmer
Carlson, Hans William
Ingelmark, Lars Rolf Bosson
Jeppsson, Lars Ingvar
Lidgard, Mats Olof Magnus
Åström, Per Håkan Albin

or Gyll, John Sören
Lund, Olof Gösta
jointly, are entitled to sign on behalf of the company.

CONTD.

1508433

PATENT- OCH REGISTRERINGSVERKET
BOLAGSAVDELNINGEN, 851 81 SUNDSVALL

CERTIFICATE OF REGISTRATION

Registration number: 556131-9608

Date of registration: 1969-12-30

Company name: Pharmacia Aktiebolag

Address:

Registered office: 171 97 STOCKHOLM
Stockholm

Share capital: SEK 6.340.955.550

FINANCIAL YEAR:
Registered financial year: 0101-1231
Latest annual report submitted covers financial period 920101-921231

DATE OF REGISTRATION OF CURRENT AND PREVIOUS COMPANY NAMES:
1993-11-17 Pharmacia Aktiebolag
1984-12-27 Procordia Aktiebolag
1969-12-30 Statsföretag Aktiebolag

SUNDSVALL 1993-12-02
Ex officio

Gunn Lahti

GUNN LAHTI

PATENT-OCH REGISTRERINGSVERKET * PRV *

(A) = employee representative
(U) = citizen of foreign country or Swedish subject residing abroad

Besöksadress:
Badhusparken

Telefon: vx 060-18 40 00
Postgiro: 95 06 08-0

Telefax: 060-12 64 77 adm
060-11 56 29 info

PATENT- OCH REGISTRERINGSVERKET
BOLAGSAVDELNINGEN, 851 81 SUNDSVALL

CERTIFICATE OF REGISTRATION

Registration number: 556029-7094

Date of registration: 1931-01-26

Company name: Kabi Pharmacia Aktiebolag

Address: 751 82 UPPSALA

FUSION:
On 29th April, 1994, the Court gave its permission for the fusion agreement to be executed. The company is thus dissolved and has merged into:

556131-9608 Pharmacia Aktiebolag

Sundsvall 1994-06-02
Ex officio

Maureen Sundin

Besöksadress:
Badhusparken

Telefon: vx 060-18 40 00
Postgiro: 95 06 08-0

Telefax: 060-12 64 77 adm
060-11 56 29 info

F 37/V1 Svart
F 37/V1 PMS 343 (Fragmin)
F 37/V1 PMS 3288 (Leaf)
F 37/V1 PMS 542 (Syringe)

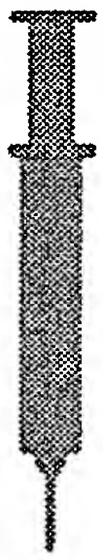
Drug substance = dalteparin sodium
Drug product = dalteparin sodium as active ingredient
Fragmin ™ (dalteparin sodium injection)

NDC 0013-2406-91

10 x 0.2 mL single dose syringes

Fragmin™

(dalteparin sodium injection)



2500 IU (anti-Xa)

For subcutaneous injection

Store at controlled room temperature 20° to 25°C (68° to 77°F) (See USP).

Caution: Federal law prohibits dispensing without prescription

Pharmacia

Fragmin™
(dalteparin sodium injection)

Fragmin™
(dalteparin sodium injection)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of

PHARMACIA AKTIEBOLAG

Patent No.: 4,303,651

Filed : January 4, 1980

Issued: December 1, 1981

Title : Heparin Fragments Having Selective Anticoagulation Activity

To the Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Transmitted herewith are the following:

Request and Application for Extension of Patent Term Under 35 U.S.C. 156 for U.S. Patent 4,303,651 (5 copies)

14 Exhibits (5 copies)

Term Calculation Sheet (5 copies)

Check No. 013001 in the amount of $1030.00

The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account 22-0185. A duplicate copy of this sheet is enclosed for the Finance Department.

Respectfully submitted,

Date: February 15, 1995

By: _____
BURTON A. AMERNICK
Registration No. 24,852
Attorney for Applicant(s)
Telephone: 202-331-7111

POLLOCK, VANDE SANDE & PRIDDY
1990 M Street, N.W., Suite 800
Washington, D.C. 20036-3425